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D. B. B. 81 (Once Amended) The compound of Claim 69, wherein one or both L are ligands of formulae (i), (ii), (iv) or (vi).

REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining in this application be allowed.

1. Amendments to the Claims

Claim 81 has been amended by replacing "and" with "or" to correct the syntax of the claim. No new matter has been added. Entry of this amendment is earnestly solicited.

2. Status of the Claims

Claims 74-83 are pending in the application. The Examiner has withdrawn Claims 75-77 and 79 from consideration as drawn to a non-elected species. If a generic claim is found allowable which encompasses the subject matter of these withdrawn claims, examination of these claims is respectfully requested. Accordingly, upon entry of the above amendments, Claims 74, 78 and 80-83 are pending for examination on the merits.

3. Rejection Under 35 U.S.C. §112

The Examiner has rejected Claim 81 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. Claim 81 has been amended, as suggested by the Examiner, to replace the conjunction "and" in the phrase "one or both L are ligands of formulae (i), (ii), (iv) and (vi)" with "or" (emphasis). Since Claim 81 has been amended to correct this defect, Applicants respectfully request that this rejection be withdrawn.

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4. Rejection Under 35 U.S.C. §103(a)

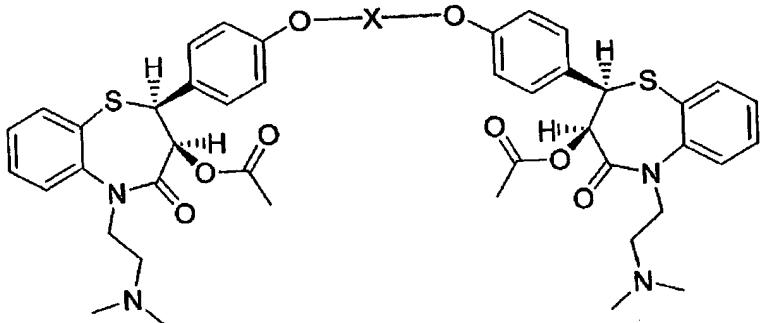
Claims 74, 78 and 80-83 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Pifferi et al. (US 5,120,730). Specifically, the Examiner suggests that the present claims are "positional isomers" or "homologs" of the compounds disclosed by Pifferi et al. Therefore, the Examiner alleges that the subject matter of the present claims is *prima facie* obvious in view of Pifferi et al. For the following reasons, Applicants respectfully disagree.

Applicants' presently claimed subject matter (i.e., Claims 74-83) is not *prima facie* obvious in view of Pifferi et al. because one skilled in the art would have no motivation to prepare the presently claimed subject matter based on the disclosure of Pifferi et al. Moreover, one skilled in the art would not have a reasonable expectation that the presently claimed subject matter would have calcium channel antagonistic activity.

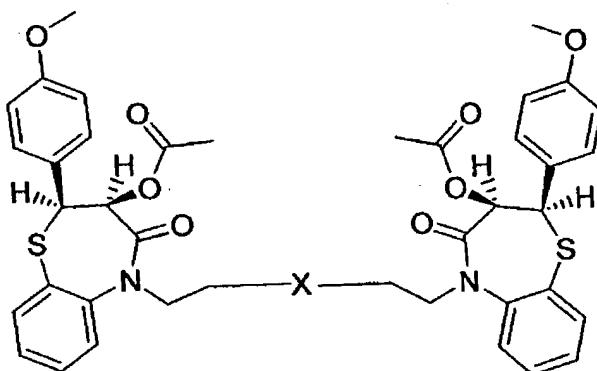
To establish a *prima facie* case of obviousness, three requirements must be satisfied. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify the references or to combine the references in a manner that produces the claimed invention. See, *In re Fine*, 837 F.2nd 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success as determined from the vantage point of the skilled artisan at the time the invention was made. See, *Amgen, Inv. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See, *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Additionally, the above teachings or suggestions, as well as the expectation of success, must come from the prior art, not from Applicants' own disclosure. See, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

In the present case, the pending claims are directed to compounds of the formula L-X-L, wherein L and X are as defined. Among the structures defined for L are formulae (vi) and (iv), which are benzothiazepine groups having different points of attachment to the linker X. For example, when both L groups are selected from formula (iv) or (vi), the resulting compounds of the present invention have the following structures:

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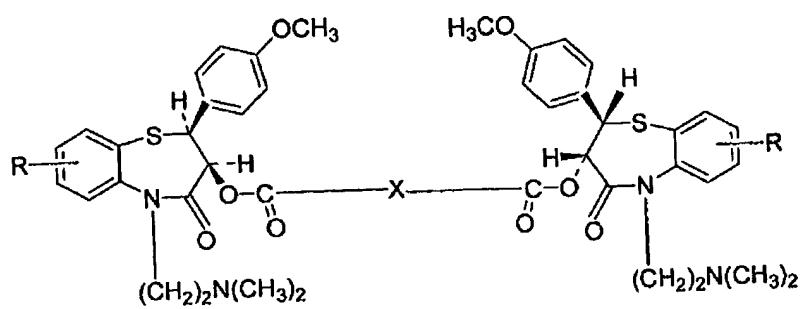


i.e., a homodimer of Applicants' formula (vi); and



i.e., a homodimer of Applicants' formula (iv).

In contrast to such compounds, Pifferi et al. teaches a generic formula in column 1, lines 30-45 as shown below.



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The Examiner has argued that Applicants' compounds are positional isomers or homologs of those disclosed by Pifferi et al., and therefore, the presently claimed compounds are *prima facie* obvious in view of Pifferi et al. For the following reasons, Applicants respectfully disagree.

First, Applicants' compounds are clearly not homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH₂- groups) of the compounds disclosed by Pifferi et al.

Second, although Applicants' compounds differ from those in Pifferi et al. by their points of attachment, their conformational structure as a whole differs significantly such that they should not be considered "positional isomers." More specifically, the orientation of the benzothiazepine moieties of Applicants' compounds is significantly different from that of Pifferi's compounds because of their different points of attachment.

As a general matter, isomerism by itself should not raise a *prima facie* case of obviousness. See *Ex parte Mowry*, 91 USPQ 219, 221 (Bd. Pat. App. 1950) (rejected the proposition that isomers in the broad sense are necessarily equivalent and held claimed cyclohexylstyrene unobvious over prior art isohexylstyrene). Similarly, the Federal Circuit has admonished against generalizing, especially in the area of chemical structural obviousness, requiring proof in the prior art to support a proposed structural change. See *In re Grabiak*, 769 F. 2d 729, 731-32, 226 USPQ 870, 872 (Fed. Cir. 1985) (finding no *prima facie* obviousness where the prior art did not suggest appellants' substitution of a thioester for an ester substituent on a carboxamide compound).

The Examiner cites *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) in her argument to establish that "compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH₂- groups) are generally of sufficient structural similarity that there is a presumed expectation that such compounds possess similar properties" and would thus be obvious."

In *In re Wilder*, (a copy of which is attached for the Examiner's convenience), the homolog compounds differed by only one -CH₂- group, and the isomers discussed were compounds with C₆-C₇ substituted alkyls differing in their branching pattern (1,4-dimethylpentyl vs. 1,3-

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dimethylbutyl or 1-methylhexyl) (page 428, column 1). The homologs and isomers of *In re Wilder* have no relevance to how Applicants' compounds differ from Pifferi et al.'s compounds.

In the present case, Pifferi et al. does not teach or suggest that the linker can be attached at a different site on the compound. Nowhere in the specification, examples, or claims of Pifferi et al. is there any suggestion that the linker can be attached at a different site on the ligand.

Similarly, although suggested by the Examiner, there is no motivation in Pifferi et al. to attach the linker to a different oxygen on the moiety. It is well known in the art that biological activity of compounds is unpredictable. Attaching the linker at a different site on the moiety would significantly change the conformational structure of the compound and the effect of such a conformational change on the compound's biological activity is highly unpredictable.

Additionally, one skilled in the art would be aware of the teachings of Inoue et al., *J. Med. Chem.*, 34(2):675-687 (1991) and Nagao et al., (*Chem. Pharm. Bull.*, 21(1):92-97 (1973), copies of which are enclosed.

Specifically, it was known by persons skilled in the art that extending the chain attached to the 3-acyloxy group (the site to which Pifferi's linker is attached) was well-tolerated. See, for example, Inoue et al. (*J. Med. Chem.*, 34(2):675-687 (1991) page 680, left column, 1st paragraph), and Nagao et al. (*Chem. Pharm. Bull.*, 21(1):92-97 (1973) pages 94-95).

However, Inoue teaches that when one or both of the methyl groups in the dimethylamino side chain are replaced by larger alkyl groups, such as an ethyl or propyl group, a *significant* decrease in potency is observed (page 680, left column, 2nd paragraph). Similarly, Nagao et al., (*Chem. Pharm. Bull.*, 21(1):92-97 (1973), Table III, page 94) noted a large decrease in activity when diethyl was substituted for dimethyl in the amino position. Given that increasing the dimethylamino side chain by adding even one additional carbon caused a significant decrease in potency, there is no motivation to use the amino site to attach larger groups, such as in Applicants' formula (vi).

In view of these teachings, one skilled in the art would not be motivated to prepare Applicants' presently claimed compounds because Pifferi et al. taught only one preferred specific linkage site; attaching the linker to a different site on the moiety would cause conformational

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changes in the resulting molecule with unknown affects on the compound's biological activity, and other references known in the art taught away from attaching the linker to the amino site.

Additionally, one skilled in the art would not have a reasonable expectation that Applicants' presently claimed compounds would have calcium channel antagonistic activity.

Specifically, Pifferi et al. teaches lower pharmacological activity for dimers. Pifferi's dimer compounds were pharmaceutically less active than the starting monomer diltiazem. When tested to control contractions on isolated rat portal vein, Pifferi's compounds had a pIC₅₀ value of 5.4 and 5.63, notably lower than the starting monomer diltiazem's pIC₅₀ value 6.09 (Table I of Pifferi et al., Column 6, lines 1-12). Based on Pifferi's results, a person skilled in the art would believe that monomers, not dimers, were more pharmaceutically useful, and thus would not be motivated to pursue modified dimers at all.

Moreover, Inoue et al. and Nagao et al. both teach a significant decrease in potency when larger substituents are attached at the amino site. Based on Inoue et al. and Nagao et al., there would be no reasonable expectation that dimers attached at the amino site would have activity.

Additionally, attaching the linker to a different site on the moiety would significantly affect the conformational structure of the compound and the effect of such a conformational change on the compound's biological activity is highly unpredictable.

Accordingly, since Pifferi et al. teaches lower pharmacological activity for dimers and prior art references such as Inoue et al. and Nagao et al. teach a decrease in activity when substituents are attached at the amino site, one skilled in the art would have no reasonable expectation of success that Applicants' presently claimed compounds would have calcium channel antagonistic activity.

Accordingly, Applicants respectfully suggest that the presently claimed subject matter is not *prima facie* obvious in view of the Pifferi et al. patent, and request that the rejection be withdrawn.

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5. Double Patenting Rejection

Claims 74 and 83 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10 and 11 of U.S. Patent No. 6,420,560.

Applicants enclose a Terminal Disclaimer, disclaiming the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of prior Patent No. 6,420,560.

Applicants respectfully request that upon filing of the enclosed Terminal Disclaimer this rejection be withdrawn.

In view of the above, Applicants respectfully submit that this application is now in condition for allowance.

Upon allowance of generic Claim 74, Applicants respectfully request that Claims 75-77 and 79, drawn to non-elected species, be rejoined with the application as provided by 37 C.F.R. §1.141 and that the application be passed promptly to allowance.

Should there be any remaining issues that can be resolved by telephone, the Examiner is respectfully requested to telephone Jeff Hagenah, an attorney of record at (650) 808-6406, or the undersigned agent at (650) 808-6144.

Respectfully submitted,

Date: Oct. 16, 2002



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MARKED-UP VERSION OF THE AMENDMENTS

In the Claims:

81. (Once Amended) The compound of Claim 69, wherein one or both L are ligands of formulae (i), (ii), (iv) and or (vi).